REMARKS

Consideration and entry of this paper, and reconsideration and withdrawal of any and all objections to and rejections of the application, and allowance of the claims, especially in view of the remarks made herein, are respectfully requested, as this paper places the application in condition for allowance, or in better condition for appeal.

I. Status of the Claims and Formal Matters

Claims 1-32 are under consideration in the present application. By this paper claims 1, 5 and 6 are amended, without prejudice.

No new matter has been added by these amendments. Support for the amendments can be found throughout the specification. Specifically, support for the limitations added to claim 1 can be found as follows. Support for the enzyme cleaving macromolecular compounds is found in original claim 13, and in Example 4 on page 13, where it is stated that the enzyme cleaves polyesters and other ester group containing polymers. Support for the enzyme of the invention being water-soluble is found on page 10 of the specification at lines 13-14, where it is stated that the enzyme is found in the supernatant culture medium. Support for the enzyme of the present invention having a molecular weight of 27,400 to 28,200 Daltons is found in the final paragraph of page 4 of the specification, and in original claim 4.

In view of the amendments to the specification, reconsideration and withdrawal of the objections to the application are therefore respectfully requested.

II. Objections to the Specification

The Disclosure was objected to because the term "GluC" was referred to on page 13 without reference to what GluC is. Applicants assert that it is well known to those of skill in the art that the GluC is an endoproteinase (*Staphylococcus aureus* Protease V8) which is a serine proteinase, and which selectively cleaves peptide bonds C-terminal to glutamic acid residues (see Drapeau, G.R., Boily, Y. and Houmard, J. (1972), Purification and properties of an extracellular protease of *Staphylococcus aureus*. *J. Biol. Chem.*, 247, 6720-6726). By this paper Applicants have amended the specification to include this description of the accepted meaning and understanding of the term "GluC" in the art. Accordingly, this objection to the specification is overcome.

III. Rejections under 35 U.S.C. §112, second paragraph

Claim 29 was rejected under 35 U.S.C. § 112 because this claim allegedly failed to further limit claim 28 on which it depends. By this paper claim 29 is cancelled, thereby overcoming this rejection.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 112, second paragraph, is respectfully requested.

IV. Rejections under 35 U.S.C. §112, first paragraph

Claims 5-6 and 20-32 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action asserted that the specification does not teach one of ordinary skill in the art how to produce a **mutant** or **derivative** or **part** of SEQ ID NO:1 that retains its enzymatic activity. Applicants respectfully disagree and traverse this rejection, for the reasons explained in the Amendment of November 4, 2004. However, in order to expedite prosecution, claims 5-6 are hereby amended to cancel the recitations of mutants, derivatives, or parts of SEQ ID NO:1 that retain enzymatic activity. By this amendment, the rejection of claims 5-6, and claims 20-32 which depend therefrom, are overcome. Applicants reserve the right to pursue claims directed to mutants, derivatives or parts of SEQ ID NO:1 that retain enzymatic activity, in later applications.

Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 112, first paragraph, is respectfully requested.

V. Rejections under 35 U.S.C. §102(b), §102(e), and §103(a)

Claims 1-6 and 10-15, were rejected under 35 U.S.C. §102 (b or e) and §103(a) as anticipated by, or in the alternative, obvious in view of Kellis et al, Kleeberg et al. or Bachmann et al.

Claims 1-6 and 10-15, 18-19, and 26-32 were rejected under 35 U.S.C. §103(a) as obvious over either Kellis et al, Kleeberg et al. or Bachmann et al.

Claims 1-15 and 18-32 were rejected under 35 U.S.C. §103(a) obvious over either Kellis et al, Kleeberg et al., or Bachmann et al., in view of Goldwasser et al.

These rejections are respectfully traversed. By the amendment to claim 1 presented herein, the rejections of claim 1, and the rejections of claims 2-15 and 18-32 which depend from claim 1, are overcome.

(A) Kellis et al.

Claim 1, as amended herein, recites an **isolated** ester-group-cleaving enzyme from ***Thermomonospora fusca***, that cleaves ester groups of **macromolecules**, is **water soluble**, and has a molecular weight of **27,400 to 28,200 Daltons**.

A two-prong inquiry must be satisfied in order for a rejection under 35 U.S.C. §102 to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue,* 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Kellis et al. fails to teach all of the elements of amended claim 1, and thus also of the remaining rejected claims, all of which depend from claim 1. The Examiner relies on the fact that Kellis et al. mentions *Thermonospora* species. However, Kellis et al. only mentions *Thermomonospora* species twice, once in claim 12, and once on the last line of column 6 where it is stated that:

> *"Similarly, it is **envisioned** that a polyesterase **may** be found in bacteria such as Bacillus spp.; Cellulomonas spp.; Clostridium spp.; Myceliophthora spp.; Pseudomonas spp., including P. mendocina and P. putida; **Thermomonospora spp**.; Thermomyces spp., including T. lanuginosa; Streptomyces spp., including S. olivochromogenes and S. scabies; and in fiber degrading ruminal bacteria such as Fibrobacter succinogenes; and in yeast including Candida spp., including C. Antarctica, C. rugosa, torresii; C. parapsllosis; C. sake; C. zeylanoides; Pichia minuta; Rhodotorula glutinis; R. mucilaginosa; and Sporobolomyces holsaticus."* (Emphasis added).

Thus, at best, Kellis teaches that *Thermomonospora* species **might** contain an esterase enzyme capable of cleaving a polyester. However, Kellis certainly does not teach that such an enzyme exists, or that it can be isolated, that it can cleave polyester or any other ester-group containing macromolecule, that is water soluble, or that it has a molecular weight of 27,400 to 28,200 Daltons, as recited by amended claim 1. Furthermore, although several of the enzymes described in Kellis et al. are shown to cleave the substrate DET (see Table 1 in column 12 of Kellis), DET is a low molecular weight ester, and not a macromolecular ester as recited in amended claim 1. The only enzyme described in Kellis et al. that is shown to cleave a macromolecule (the macromolcule PET) is a cutinase enyzme from *Pseudomonas mendocina* (see Table 1 in column 12 of Kellis). This cutinase enzyme is not an esterase enzyme according to the present invention. This is evident from the fact that the sequence of cutinase (as drawn from claim 1 of U.S. Patent No. 5,389,536, a copy of which is submitted herewith) shows less than 30% homology to the enzymes of the present invention. A sequence alignment demonstrating the low level of homology between the *Pseudomonas mendocina* cutinase and the *Thermomonospora fusca* esterase, is submitted herewith. In addition, this cutinase enzyme has a different optimum pH range to the enzymes of the present invention. Thus, Sebastian & Kolattukudy demonstrated that this cutinase has an optimal pH range of 8.5-10.5 (see the right-hand column of Sebastian & Kolattukudy, Arch. Biochem. Biophys 263 (1988) p 77-85, a copy of which is submitted herewith). This is in contrast to the enzyme of the present invention which has an optimal pH range of 6-7. Furthermore, this cutinase enzyme is not isolated from *Thermomonospora fusca.* Accordingly, Kellis et al. fails to teach the *Thermomonospora fusca* ester-group cleaving enzymes of the present invention.

Thus, the teaching of Kellis et al. fails both the first and second prongs of an enquiry under 35 U.S.C. §102 since it fails to teach every element of the rejected claims, and fails to provide an enabling disclosure of the claimed enzyme.

The Examiner further asserts that the teaching of Kellis et al. would have rendered it obvious for one of skill in the art to isolate and purify the *Thermomonospora* enzymes of the present invention. Applicants respectfully disagree.

It is well-settled that for a rejection under 35 U.S.C. §103 to stand there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the teachings of the cited prior art. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed.

Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Furthermore, the Examiner is respectfully reminded that "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applying the above standard, Kellis et al. fails to render the present claims obvious under 35 U.S.C. §103(a). The argument that one of skill in the art would find it obvious to try and isolate the enzyme of the present invention after having read the disclosure of Kellis et al. fails because Kellis et al. provides no motivation for isolating such an enzyme, and no expectation of success in isolating such as enzyme, as follows. Firstly Kellis does not provide any evidence that a polyester cleaving enzyme even exists in *Thermomonospora* species. Secondly, since Kellis fails to teach that such an enzyme, if it existed, might be water-soluble, one of skill in the art would not be motivated to look for such an enzyme in the culture supernatant. Thirdly, the fact that out of 51 enzymes tested by Kellis et al. only one enzyme was able to cleave the macromolecule PET, and that out of 29 esterase enzymes tested **none** were able to cleave the macromolecule PET, demonstrates that one of skill in the art would not be motivated to look for, and would have no expectation of success in isolating, an enzyme from *Thermomonospora* capable of cleaving such macromolecules. The only enzyme demonstrated by Kellis et al. to cleave the macromolecule PET was a cutinase. This cutinase enzyme is not an esterase enzyme according to the present invention. This is evident from the fact that the sequence of cutinase (as drawn from claim 1 of U.S. Patent No. 5,389,536, a copy of which is submitted herewith) shows less than 30% homology to the enzymes of the present invention. In addition, this cutinase enzyme has a different optimum pH range to the enzymes of the present invention. Thus, Sebastian & Kolattukudy demonstrated that this cutinase has an optimal pH range of 8.5-10.5 (see the right-hand column of Sebastian & Kolattukudy, Arch. Biochem. Biophys 263 (1988) p 77-85, a copy of which is submitted herewith). This is in contrast to the enzyme of the present inventions which has an optimal pH range of 6-7. Furthermore, this cutinase enzyme is not

isolated from *Thermomonospora fusca.* Accordingly, upon reading Kellis et al., one of skill in the art would not be motivated to look for, and would have no expectation of success in isolating, an enzyme from *Thermomonospora* capable of cleaving the ester groups of macromolecules as recited in the present claims.

Furthermore, the combination of Kellis et al. and Goldwasser el al. also fails to render the present claims obvious. Goldwasser et al. allegedly teaches how to produce polyclonal and monoclonal antibodies and hybridomas against a given protein. The Examiner contends that it would have been obvious to one of ordinary skill in the art to isolate the enzyme of the present invention, and then to use the teachings of Goldwasser et al. to produce an antibody to that enzyme. However, as described above, the enzymes of the present invention are novel, and are not obvious over Kellis et al. Therefore, antibodies directed to the enzymes of the present invention are also novel and not obvious, regardless of whether Goldwasser does, or does not, teach how to produce an antibody that recognizes a protein.

(B) Kleeberg et al.

Kleeberg et al. describe the use of a culture of intact *Thermomonospora fusca* cells to degrade the polyester BTA 40:60 (see page 1734, left column, line 18). However, Kleeberg et al. fails to teach all of the elements of the rejected claims and therefore fails to anticipate the present claims under 35 U.S.C. §102.

At best, Kleeberg teaches that intact cells of *Thermomonospora* possess a polyester cleaving activity. However, Kleeberg does not teach that this activity is the result of a single enzyme, does not teach that such an enzyme might function in a cell-free situation, does not teach that such an enzyme might be water-soluble as opposed to lipid-soluble, does not teach that such an enzyme might be found in the culture supernatant, does not teach or suggest that such an activity can be isolated or purified from the culture supernatant, and does not teach or suggest that such an enzyme has a molecular weight of 27,400 to 28,200 Daltons. Thus, the teaching of Kleeberg et al. fails both the first and second prongs of an enquiry under 35 U.S.C. §102, since it fails to teach every element of the rejected claims, and fails to provide an enabling disclosure of the isolated enzyme of the rejected claims.

The Examiner asserts that the teaching of Kleeberg et al. would also have rendered it obvious for one of skill in the art to isolate and purify the *Thermomonospora* enzymes of the present invention. Applicants respectfully disagree.

As described above, it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the teachings of the cited prior art, and "obvious to try" is not the appropriate standard for determining obviousness under 35 U.S.C. §103. Prior to the present invention, and at the time of Kleeberg et al., the understanding in the art was that the polyester cleavage activity of *Thermomonospora fusca* was a cell-bound enzymatic activity. There was no teaching in Kleeberg that this activity was the result of a water-soluble molecule that could be found un-associated with cells, such as in the supernatant of a *Thermomonospora fusca* culture. The fact that Kleeberg et al. used an entire *Thermomonospora fusca* cell suspension to perform their degradation experiments, as opposed to using just the culture supernatant of the *Thermomonospora* cells is consistent with the view that the activity was believed to be a cell-bound, and not a water-soluble, enzyme. Furthermore, the fact it was known at the time of Kleeberg that lipases had polyester-cleaving activity (see Kleeberg page 1734) underscores the surprising nature of the findings of the present invention, since prior to the present invention, lipases were thought to be cell-bound enzymes and not water-soluble enzymes.

Thus, Kleeberg et al. does not provide any expectation that the polyester-cleaving enzyme activity of *Thermomonospora* cells may be the result of a single enzyme molecule, or that such a molecule might function in a cell-free situation. Similarly, since Kleeberg et al. fails to teach what size such an enzyme molecule might be, or whether such an enzyme might be water-soluble or lipid-soluble, one of skill in the art would have no expectation of success in isolating such an enzyme from the supernatant of a culture of Thermomonospora cells.

Furthermore, the combination of Kleeberg et al. and Goldwasser et al. also fails to render the present claims obvious. Goldwasser et al. allegedly teaches how to produce polyclonal and monoclonal antibodies and hybridomas against a given protein. The Examiner contends that it would have been obvious to one of ordinary skill in the art to obtain the enzyme of the present invention, and to use the teachings of Goldwasser et al. to produce an antibody to such a protein. However, as described above, the enzymes of the present invention are novel and are not obvious. Therefore, antibodies directed to the enzymes of the present invention are also novel and not obvious, regardless of whether Goldwasser teaches or does not teach a general method for producing antibodies against proteins.

(C) <u>Bachmann et al.</u>

The Office Action alleges that Bachmann et al. teaches the isolation of xylanases, endoxylanases, α-arabinofuranosidases and acetyl esterases from *Thermomonospora* species, and asserts that these enzymes are all ester-group-cleaving enzymes. The Examiner asserts that, "absent very convincing proof to the contrary" the enzymes of Bachmann et al. are the same as those of the present invention, and thus render the present claims unpatentable under 35 U.S.C. §102. Applicants respectfully traverse this rejection.

Firstly, the Examiner's assertion that all of these enzymes are acetyl esterases is incorrect. As described on page 2122 of Bachmann et al (see left hand column under the heading "Enzyme Assays") these are in fact three distinct enzymes activities which are assayed in different ways. Thus, Bachmann et al. describes separate and distinct xylanase activities (which includes endoxylanas activities), arabrabinofuranosidase activities, and acetyl esterase activities. Of these three, only the third type of enzyme activity, i.e. the acetyl esterase activity, could be the result of an ester-group-cleaving enzyme.

Secondly, the ester-group-cleaving enzymes described and claimed in the present application are distinct from those described by Bachmann et al. Thus, Bachmann et al. describes three distinct forms of acetyl esterase enzyme, an 80 kDa isoform, a 40 kDa isoform, and a 20 kDa isoform (see page 2125 to 2126 of Bachmann et al.). Thus, these proteins are distinct from the ester-group-cleaving enzymes of the present invention, which have a molecular weight of between 27.4 to 28.2 kDa. By this paper claim 1 has been amended to specify the molecular weight of the novel ester-group-cleaving enzymes of the present invention, thereby overcoming the rejection over Bachmann et al.

The Examiner further asserts that the teaching of Buchmann et al. would have rendered it obvious for one of skill in the art to isolate and purify the *Thermomonospora* enzymes of the present invention. Applicants respectfully disagree.

As described above, it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the teachings of the cited prior art. Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure.

Buchmann teaches that three acetyl esterases having molecular weights of 20, 40, and 80 kDa are produced by *Thermomonospora* cells, and teaches that the 20, 40 kDa forms are found

extracellularly in the culture supernatant. Buchmann et al. provides no suggestion that other ester-group-cleaving enzymes might also be found. Thus, one of skill in the art would not be motivated to look for, and would have no expectation of success in finding, other ester-group-cleaving enzymes in the supernatant of *Thermomonospora* cultures. The discovery by the Applicants of a new 27.4-28.2 kDa ester-group cleaving enzyme was therefore unexpected and surprising. Accordingly, the claims of the present application, as amended herein, are not obvious over the teaching of Bachmann et al.

Furthermore, the combination of Bachmann et al. and Goldwasser el al. also fails to render the present claims obvious. Goldwasser et al. allegedly teaches how to produce polyclonal and monoclonal antibodies and hybridomas against a given protein. The Examiner contends that it would have been obvious to one of ordinary skill in the art to try to isolate the enzyme of the present invention, and would have been obvious to use the teachings of Goldwasser et al. to produce an antibody to the enzyme of the present invention. However, as described above, the enzymes of the present invention are novel, and are not obvious over Bachmann et al. Therefore, antibodies directed to the enzymes of the present invention are also novel and not obvious, regardless of whether Goldwasser does, or does not, teach how to produce an antibody that recognizes a given protein.

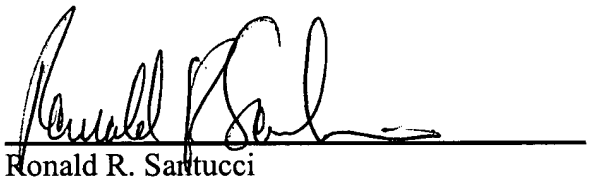
Accordingly, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. §102(b), §102(e) and §103(a), is respectfully requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance, or in better condition for appeal. Entry of this paper, favorable reconsideration of the application, and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: 

Ronald R. Santucci
Reg. No. 28,988
(212) 588-0800